ATTACHMENT A

REMARKS

Claims 89-127 are pending in the present application. By this Amendment, Applicants have amended claims 89, 125 and 126; and added new claim 127. Applicants respectfully submit that the present application is in condition for allowance based on the discussion below.

Claim 123 was subject to a Restriction Requirement as being drawn to a separate invention from the invention of claims 89-122 and 124-126. Without addressing the merits of the Restriction Requirement to claim 123, Applicants have canceled claim 123 without prejudice or disclaimer.

Claims 89-122 and claims 124-126 were rejected under 35 U.S.C. § 112, second paragraph. Specifically, claim 89 was rejected as being ambiguous. Further, claims 125 and 126 were rejected as being ambiguous for reciting the treatment of a CNS disorder which includes obesity.

By this Amendment, Applicants have amended claim 89 to more clearly recite the method of treating a disease or condition from the claimed diseases or disorders using a compound having the general formula (IIa). In addition, Applicants have amended claim 125 to remove reference to obesity and have added a new claim 127 drawn to the treatment of obesity using the compound of general formula (IIa). Accordingly, Applicants respectfully submit that the amendments to claims 89 and 125 obviate the rejection to the claims under 35 U.S.C. 112, second paragraph.

Claims 89-122 and claims 124-126 were rejected under 35 U.S.C. § 112, first paragraph for containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to practice the invention. Specifically, the Examiner alleges that the present disclosure does not enable one skilled in the art to practice the invention based on the claim linked to the ligand of the histamine H3 receptors by use of a multitude of compounds having a nitrogen atom as a core. Further, the Examiner alleges that the state of the "prior art does not link all of the diseases/conditions listed in the claims to a ligand of the histamine H3 receptors". In addition, the Examiner asserts that the previously submitted declaration of 22 November 2002 which discloses compound 117,3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, is non-commensurate with the scope of claims 89-122 and 124-126 as the declaration enables the compound 117 but does not enable any of the other compounds claimed.

Contrary to the Examiner's allegation, the claims are fully supported by the specification as filed to enable one of ordinary skill in the art to practice the invention as claimed. Therefore, no undue experimentation is necessary in order to practice the invention as claimed.

The present invention is based on the discovery by the present inventors that the claimed compounds can inhibit the binding of histamine to its H3 receptor. The H3 receptor is mainly responsible for regulating synthesis and release of histamine in the synaptic gap; the inhibition therefore leads to higher rates of histamine release.

In order to be a suitable medicament, the candidate compounds must show the following activities:

- the ability to inhibit the binding of histamine to H3 receptor,
- the ability to be orally administered, and
- the ability to cross the bloodbrain barrier.

The oral administration, bloodbrain barrier crossing and H3 receptor ligand activities can be evaluated on an *in vivo* animal model. H3 ligand activity can be tested by measuring the telemethyl histamine levels. Telemethyl histamine is the major metabolite of histamine and the increase of its tissue levels reflects an increase of histamine release and action. The compounds to be tested were orally administered to mice, and the telemethyl histamine level was then measured.

Compound of Example 117 was found active in this animal model and its activity was then confirmed in human patients (see the declaration previously filed with the Amendment of January 22, 2003). Consequently, this confirmation validates the animal model used.

As a result, the animal pharmacological model enables to predict that the compounds active in this test will have the desired activity in human patients.

As requested by the Examiner, these examples provide evidence herewith that the compounds of the invention are active in this *in vivo* animal test, as apparent from the results listed below.

ID 50 is expressed in mg/kg, following oral administration. The results below are given to illustrate the activity shown by the claimed compounds.

Examples	ED50 (mg/kg)
1	6.9
2	3.4
18	1.1
22	1.9
23	4.5
26	2.8
27	6.6
37	5.1
38	1.3
39	1.5
40	2.6
42	1.5
43	0.5
44	4.4
45	3.6
46	0.44
47	2
49	1.7
50	1
51	3
52	2
54	3.3
56	1.1
58	1.6
59	0.2
60	0.64
61	4.2
63	0.45
64	0.73
65	1.1
66	0.34
67	0.12
68	0.49
69	0.6
70	3.5
71	4.2
72	0.5
73	0.47
74	0.21
75	2.2
76	0.18
78	0.77

79	0.36
81	0.67
82	1.3
83	0.78
84	0.53
85	4.9
86	0.82
87	1.6
88	0.14
89	1.3
90	0.59
91	1.7
93	0.85
94	1.8
95	2.6
96	0.83
97	1.5
98	4.5
99	3.4
100	0.39
101	0.17
102	2.1
103	2.3
104	0.3
105	3.4
106	4
107	2.5
108	3.3
109	3.1
110	2.4
111	0.92
112	1.6
113	0.54
114	1.2
116	3.7
117	1.6
127	3.9
128	1.9
133	3.8
137	3.4
140	0.78
141	5.9
143	3.2
148	5.5
149	2.8

163	2.7

Consequently, it is apparent from the results given above that the exemplified compounds of the invention show an *in vivo* activity similar or even better that compound of example 117. The clinical test carried out with respect to the compound of example 117 in human patient provides evidence that animal test are predictable of human activity. Consequently, the *in vivo* results given above provide evidence that the compounds of the invention are active on human.

For the sake of completeness, it is respectfully noted that all the conditions listed in claim 89 derive from the H3 receptor activity. This was comprehensively discussed in the previously filed declaration filed January 22, 2003.

In order to assist the Examiner in locating the enabling disclosure in the specification, the following table summarizes the disclosure of the link between H3 receptor activity with the diseases and conditions listed in claim 89, with reference to articles numbered as 1-10 in the previously filed declaration of January 22, 2003.

Diseases or conditions of claim 89	Disclosure in Articles 1-10 of the declaration
CNS disorders	1
CNS disorders in aged persons	8 (abstract)
Psychotropic	6 (p. 403)
wakefulness, attention, memory, mood	1 (p. 27), 6 (p. 401), 7 (abstract), 8 (title + abstract), 1 (p. 30)
Obesity	1 (p. 29), 6 (p. 402)
Vertigo, motion sickness	1 (p. 27), 8 (abstract)
sedative, tranquility, anti-stress	1 (p. 27), 1 (p. 29)
Analgesic	1 (p. 27)
Antimigrane	1 (p. 27), 4,3 (abstract)
psychosomatic	6 (p. 403)
respiratory, inflammatory, allergic, rheumatic conditions, asthma, inflammatory disorders, bronchitis, rhinitis, tracheitis, gastric or duodenal ulcers, ulcerative colitis, Crohn's disease, irritable bowel syndrome, cystitis, metritis, urinary and fecal incontinence, urticaria, itching, arthritis, conjunctivitis, premenstrual syndrome	4,3 (abstract), 5 (abstract)

Consequently, the Applicants have provided evidence in respect of the two following aspects:

- the compounds of the invention exhibit *in vivo* activity on animals; this *in vivo* activity is predictable of the activity on human patients; and
- the activities on the compounds of the invention on the conditions listed in claim 89 are clearly linked with the demonstrated H3 activity.

As a result, the Applicants have shown evidence that the breadth of the claims with respect to the definition of compounds, as well as with respect to the number of these conditions is commensurate with the nature of the invention. The results of working examples, provided herewith, together with the prior art reciting the link between H3 receptor and conditions make the activities of the compounds as claimed,

predictable. Consequently, based on the content of the disclosure of the prior art, the skilled person is provided with enough direction to work the invention and thus, the claimed invention is enabled in accordance with 35 U.S.C. § 112, first paragraph.

Based on the foregoing discussion, Applicants respectfully submit that the specification fully supports the claims to enable one of ordinary skill in the art to practice the invention and therefore, Applicants respectfully request that the rejection to the claims under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim 126 was objected to under 37 C.F.R. § 1.73 as being a substantial duplicate of claim 125. In the Amendment of January 22, 2003, Applicants inadvertently introduced a clerical error in the marked up copy of the claims in which claim 126 was written as an exact duplicate of claim 125. However, the clean copy version of the claims included the correct claim 126. By this Amendment, in Applicants' Attachment B, claim 126 is properly written as was provided in the previous clean copy of the claims. Therefore, Applicants respectfully request that the double patenting rejection to claim 126 be withdrawn.

In view of the foregoing, Applicants respectfully submit that the present application is now in a condition for immediate allowance.

END REMARKS

ATTACHMENT B
Amendments to the Claims

Please cancel claim 123 without prejudice or disclaimer; and add new claim 127.

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-88. (Cancelled)

89. (Currently Amended) A method of treating diseases or conditions selected from the group consisting of

~~treating~~ central nervous system disorders~~;~~, CNS disorders in aged persons;

~~providing~~ psychotropic ~~effects, promoting~~, nootropic, wakefulness, attention, memory and ~~improving~~ mood disorders;

~~providing nootropic effects;~~

~~treating~~ obesity, vertigo and motion sickness;

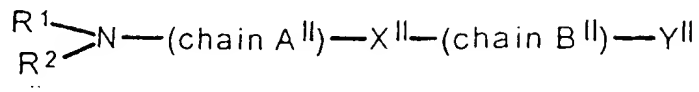
~~treating CNS disorders including CNS in aged persons;~~

~~providing~~ conditions requiring sedative, tranquilizing, anti-stress, analgesic and antimigraine ~~activity~~ treatment;

~~treating~~ psychosomatic disorders, respiratory, allergic and rheumatic conditions of inflammatory conditions of the eye, urogenital system, digestive tract, skin, respiratory system and bronchi; and

~~treating~~ asthma, bronchitis, rhinitis, tracheitis, gastric or duodenal ulcers, ulcerative colitis, Crohn's disease, irritable bowl syndrome, cystitis, metritis, urinary and faecal incontinence, urticaria, itching, arthritis, conjunctivitis and premenstrual syndrome;

using a compound having the general formula (IIa)



(IIa)

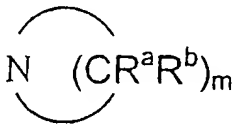
wherein:

R^1 and R^2 may be identical or different and represent each independently

- a lower alkyl or cycloalkyl,

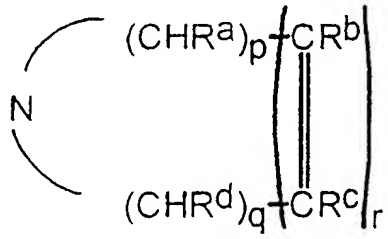
or taken together with the nitrogen atom to which they are attached,

- a saturated nitrogen-containing ring

i) 

with m ranging from 2 to 8, or

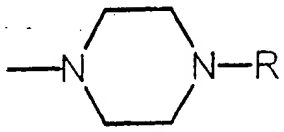
- a non-aromatic unsaturated nitrogen-containing ring

ii) 

with p and q being 0 to 3 independently and r being from 0 to 4, provided that p and q are not simultaneously 0 and $2 \leq p + q + r \leq 8$,

R^{a-d} being independently a hydrogen atom or a lower alkyl, cycloalkyl, or carboalkoxy group, or

- a morpholino group, or
- a N-substituted piperazino group:



with R being a lower alkyl, cycloalkyl, carboalkoxy, aryl, arylalkyl, an alkanoyl or aroyl group; and

(i) the chain A^{II} selected from a saturated or unsaturated, straight or branched hydrocarbon chain containing 1 to 6 carbon atoms, the saturated hydrocarbon chain optionally may be interrupted by a hetero atom which may be a sulphur atom;

(ii) X^{II} selected from an oxygen atom, sulphur atom, -NH-, -NHCO-, -N(alkyl)CO-, -NHCONH, -NH-CS-NH-, -NHCS-, -O-CO-, -CO-O-, -OCONH-, -OCON(alkyl)-, -OCON(alkene), -OCONH-CO-, -CONH-, -CON(alkyl)-, -SO-, -CO-, -CHOH-, -N(saturated or unsaturated alkyl), -S-C(=NY^{II})-NH-Y^{II}- with the Y^{II} identical or different, and -$NR_{II}C(=NR^{II}_{II})$-NR^{I}_{II}- where R_{II} AND R^{I}_{II} denote a hydrogen atom or a lower alkyl radical and R^{II}_{II} denotes a hydrogen atom or another powerful electronegative group, which may be selected from a cyano or COY_1^{II} group, Y_1^{II} denoting an alkoxy group;

(iii) the chain B^{II} selected from an aryl; arylalkyl; arylalkanoyl group; a straight alkylene chain -$(CH_2)_{nII}$-, n being an integer which can vary between 1 and 5 or a branched alkylene chain containing from 2 to 8 carbon atoms, the alkylene chain being optionally interrupted by one or a number of oxygen or sulphur atoms; and a group -$(CH_2)_{nII}$-O- or -$(CH_2)_{nII}$-S- where n_{II} is an integer equal to 1 or 2; and

(iv) Y^{II} selected from a straight or branched alkyl group containing 1 to 8 carbon atoms; a cycloalkyl containing 3 to 6 carbon atoms; a bicycloalkyl group; a cycloalkenyl group; an aryl group such as an optionally substituted phenyl group; a 5- or 6-membered heterocyclic radical containing one or two heteroatoms chosen from nitrogen and sulphur atoms, the heterocyclic radical optionally being substituted; and a bicyclic radical resulting from the fusion of a benzene ring to a heterocycle as defined above;

or

(i') the chain A^{II} selected from an unbranched, branched or unsaturated alkyl group $-(CH_2)_{nII}-$ where n_{II} is an integer which can vary between 1 and 8; an unbranched or branched alkene group comprising from 1 to 8 carbon atoms; and an unbranched or branched alkyne group comprising from 1 to 4 carbon atoms;

(ii') the group X^{II} selected from -OCONH-, OCON(alkyl)-, -OCON(alkene)-, -OCO-, -OCSNH-, $-CH_2-$, -O-, $-OCH_2CO-$, -S-, -CO-, -CS-, armine, and saturated or unsaturated alkyl;

(iii') the chain B^{II} selected from an unbranched, branched or unsaturated lower alkyl comprising from 1 to 8 carbon atoms; $-(CH_2)_{nII}$(hetero atom)- where the hetero atom is preferably a sulphur or oxygen atom; n_{II} being an integer which can vary between 1 and 5; and

(iv') the group Y^{II} represents a phenyl group, unsubstituted or mono- or polysubstituted with one or more identical or different substituents selected from halogen atoms, OCF_3, CHO, CF_3, $SO_2N(alkyl)_2$ such as $SO_2N(CH_3)_2$, NO_2, S(aryl), SCH_2(phenyl), an unbranched or branched alkene, an unbranched or branched alkyne

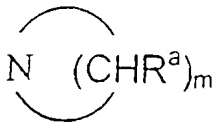
optionally substituted with a trialkylsilyl radical, -O(alkyl), -O(aryl), -CH_2CN, a ketone, an aldehyde, a sulphone, an acetal, an alcohol, a lower alkyl, -CH=CH-CHO, -C(alkyl)=N-OH, -C(alkyl)=N-O(alkyl) and other keto derivatives, -CH=NOH, -CH=NO(alkyl), and other aldehyde derivatives, -C(alkyl)=NH-NH-$CONH_2$, an O-phenyl or -OCH_2(phenyl) group, -C(cycloalkyl)=NOH, -C(cycloalkyl)=N-O(alkyl); an optionally substituted heterocycle; ; a cycloalkyl; a bicyclic group and preferably a norbomyl group; a phenyl ring fused to a heterocycle comprising a nitrogen hetero atom or to a carbocycle or a heterocycle bearing a keto function; an unbranched or branched lower alkyl comprising from 1 to 8 carbon atoms; an unbranched or branched alkyne comprising from 1 to 8 carbon atoms and preferably 1 to 5 carbon atoms; a linear or branched alkyl mono- or polysubstituted with phenyl groups which are either unsubstituted or mono- or polysubstituted; a phenyl alkyl ketone in which the alkyl group is branched or unbranched or cyclic; a substituted or unsubstituted benzophenone; a substituted or unsubstituted, unbranched or branched or cyclic phenyl alcohol; an unbranched or branched alkene; a piperidyl group; a phenylcycloalkyl group; a polycyclic group, in particular a fluorenyl group, a naphthyl or polyhydronaphthyl group or an indanyl group; a phenol group; a ketone or keto derivative; a diphenyl group; a phenoxyphenyl group; a benzyloxyphenyl group,

or its pharmaceutically acceptable salts, hydrates, or hydrated salts, or the polymorphic crystalline structures of these compounds or their optical isomers, racemates, diastereoisomers or enantiomers, as a ligand of the histamine H_3-receptors, wherein a patient in need thereof is treated with an effective amount.

90. (Previously Presented) The method according to claim 89, wherein R^1 and R^2 are independently a lower alkyl group.

91. (Previously Presented) The method according to claim 90, wherein R^1 and R^2 are each an ethyl group.

92. (Previously Presented) The method according to claim 89, wherein $-NR^1R^2$ is a saturated nitrogen-containing ring:

i) 

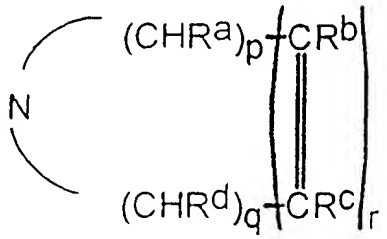
m being as defined in claim 89.

93. (Previously Presented) The method according to claim 92, wherein m is 4, 5 or 6.

94. (Previously Presented) The method according to claim 93, wherein $-NR^1R^2$ is a piperidyl group.

95. (Previously Presented) The method according to claim 93, wherein $-NR^1R^2$ is a pyrrolidinyl group.

96. (Previously Presented) The method according to claim 89, wherein $-NR^1R^2$ is a non-aromatic unsaturated nitrogen-containing ring:

ii) 

R^{a-d} and p, q and r being defined in claim 89.

97. (Previously Presented) The method according to claim 96, wherein p, q and r are 1 or 2.

98. (Previously Presented) The method according to claim 97, wherein p is 2 and q and r are 1.

99. (Previously Presented) The method according to claim 92, wherein R^{a-d} are each a hydrogen atom.

100. (Previously Presented) The method according to claim 93, wherein R^{a-d} are each a hydrogen atom.

101. (Previously Presented) The method according to claim 94, wherein R^{a-d} are each a hydrogen atom.

102. (Previously Presented) The method according to claim 95, wherein R^{a-d} are each a hydrogen atom.

103. (Previously Presented) The method according to claim 96, wherein R^{a-d} are each a hydrogen atom.

104. (Previously Presented) The method according to claim 97, wherein R^{a-d} are each a hydrogen atom.

105. (Previously Presented) The method according to claim 92, wherein the nitrogen-containing ring i) or ii) is one of mono- and di-substituted.

106. (Previously Presented) The method according to claim 105 wherein the nitrogen-containing ring i) or ii) is mono-substituted with an alkyl group.

107. (Previously Presented) The method according to claim 105, wherein the nitrogen-containing ring is mono-substituted with a methyl group.

108. (Previously Presented) The method according to claim 105, wherein the substituent(s) is(are) in meta-position with respect to the nitrogen atom.

109. (Previously Presented) The method according to claim 89, wherein $-NR^1R^2$ is a morpholino group.

110. (Previously Presented) The method according to claim 89, wherein $-NR^1R^2$ is a N-substituted piperazino group.

111. (Previously Presented) The method according to claim 110, when the piperazino group is N-acetylpiperazino.

112. (Previously Presented) The method according to claim 89, wherein X^{II} is selected from -O-, -NH-, $-CH_2-$, -OCONH-, -NHCO-, and -NHCONH-.

113. (Previously Presented) The method according to claim 112, wherein X^{II} is -O-.

114. (Previously Presented) The method according to claim 89, wherein Y^{II} is selected from a linear or branched alkyl group; a cycloalkyl group which may be selected from a particular cyclopentyl and cyclohexyl group; a phenyl group unsubstituted or mono-substituted; a heterocyclic radical; and a bicyclic radical.

115. (Previously Presented) The method according to claim 114, wherein Y^{II} comprises a phenyl group unsubstituted or mono-substituted.

116. (Previously Presented) The method according to claim 89, wherein Y^{II} represents a phenyl group at least mono-substituted with a keto-substituent which may

include a linear or branched chain aliphatic ketone comprising from 1 to 8 carbon atoms and optionally bearing a hydroxyl group, a cycloalkylketone, an aryl alkyl ketone or arylalkenylketone in which the aryl group is optionally substituted, or a heteroaryl ketone.

117. (Previously Presented) The method according to claim 89, wherein Y^{II} is a phenyl group at least mono-substituted with -CHO, a ketone, an aldehyde, -CH=CH-CHO, -C(alkyl)=N-OH, -C(alkyl)=N-O(alkyl) and other keto derivatives, -CH=N-OH, -CH=NO(alkyl) and other aldehyde derivatives, -C(cycloalkyl)=NOH, -C(cycloalkyl)=N-O(alkyl).

118. (Previously Presented) The method according to claim 89, wherein chain A^{II} is a chain $-(CH_2)_{nII}-$ with n varying from 1 to 6, preferably from 1 to 4.

119. (Previously Presented) The method according to claim 118, wherein the chain A^{II} is $-(CH_2)-$.

120. (Previously Presented) The method according to claim 89, wherein the chain B^{II} is $-(CH_2)_2-$ or $-(CH_2)_3-$.

121. (Previously Presented) The method according to claim 89, wherein X is an oxygen atom, the chain A^{II} and chain B^{II} are both $-(CH_2)_3-$.

122. (Previously Presented) The method according to claim 89, wherein the compound is selected from:

- 3,3-Dimethylbutyl 3-piperidinopropyl ether
- 3-Phenylpropyl 3-piperidinopropyl ether
- 3-(4-Chlorophenyl)propyl 3-piperidinopropyl ether
- 2-Benzothiazolyl 3-piperidinopropyl ether
- 3-Phenylpropyl 3-(4-methylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3,5-cis-dimethylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3,5-trans-dimethylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3-methylpiperidino)propyl ether
- 3-Phenylpropyl 3-pyrrolidinopropyl ether
- 3-(4-Chlorophenyl)propyl 3-(4-methylpiperidino)propyl ether
- 3-(4-Chlorophenyl) propyl 3-(3,5-cis-dimethyl piperidino)propyl ether
- 3-(4-Chlorophenyl) propyl 3-(3,5-trans-dimethyl piperidino)propyl ether
- 3-Phenylpropyl 3-(N,N-diethylamino)propyl ether
- N-Phenyl-3-piperidinopropyl carbamate
- N-Pentyl-3-piperidinopropyl carbamate
- (S)-(+)-N-[2-(3,3-Dimethyl)butyl]-3-piperidinopropyl carbamate
- 3-Cyclopentyl-N-(3-(1-pyrrolidinyl)propyl)propanamide
- N-Cyclohexyl-N'-(1-pyrrolidinyl-3-propyl)urea
- 2-((2-Piperidinoethyl)amino)benzothiazole
- 5-Piperidinopentylamine
- 2-Nitro-5-(6-piperidinohexyl)pyridine

- 3-Nitro-2-(6-piperidinohexylamino)pyridine
- 2-(6-Piperidinohexylamino)pyrimidine
- N-(6-Phenylhexyl)piperidine
- N-phenyl-N'-(diethylamino-3-propyl)urea
- N-benzyl-N'-(3-piperidinopropyl)guanidine
- N-(3-(N,N-Diethylamino)propyl)N'-phenylurea
- N-Cyclohexylmethyl-N'-(3-piperidinopropyl)guanidine.

123. (Canceled)

124. (Previously Presented) The method of treatment according to Claim 89 wherein the heterocycle comprises a sulphur hetero atom.

125. (Currently Amended) The method of treatment according to Claim 89 wherein the central nervous disorders treated are selected from the group consisting of Alzheimer disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, ~~obesity,~~ vertigo and motion sickness.

126. (Previously Presented) The method of treatment according to Claim 89 wherein the nootropic effects treatment includes use in a treatment to stimulate attention and memorization capacity.

127. (New) The method of treatment according to claim 89 wherein the condition treated with the compound of general formula (IIa) is obesity.